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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/115,589	07/15/1998	JENNIFER E. VAN EYK	12917	1553

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/115,589	VAN EYK ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-84 and 87-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-84 and 87-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 December 2006 has been entered.

Formal Matters

Claims 80 and 97 are amended. Claims 85-86 and 99-102 are canceled. Claims 80-84 and 87-98 are under consideration.

Rejections Withdrawn

Claim Rejections - 35 USC § 102

The rejection of claims 80, 81, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96 under 35 U.S.C. 102(a) as being anticipated by Takahashi et al. (Reference #7 on Applicants' 1449 form submitted 21 January 2004) is withdrawn in response to Applicants' amendment of the claims to specifically recite the binding activity required by the antibody or antibody fragment in the amendment to claim 80 filed 19 December 2006.

Specifically, the antibody taught by Takahashi does not bind a peptide fragment, as now required by the claim.

Claim Rejections - 35 USC § 103

The rejection of claims 80-84 and 87-98 under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. as applied to claims 80, 81, 87, 88, 89, 90, 91, 92, 93, 94, 95 and 96 above, and further in view of Westfall et al. (cited in Office actions mailed 7 April 2004, 13 January 2005 and 29 December 2005) is withdrawn in response to Applicants' amendment of claim 80 to specifically recite the binding activity required by the antibody or antibody fragment in the amendment to claim 80 filed 19 December 2006 stated above. Furthermore, Westfall et al. (Circ. Res. 1992; 70: 302-313—on Applicants' 1449 form dated 22 October 2004) teach the JLT-12 monoclonal antibody for the detection of TnT, however, all the tissues are isolated from heart, not skeletal muscle, thus do not support an obviousness rejection over the instant claims.

New Rejections/Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-84 and 87-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for a method of

assessing skeletal muscle damage in a subject comprising detecting hypoxemia-induced skeletal troponin I (sTnI) peptide fragment with a molecular mass of 17 kDa and/or a 42 kDa covalent complex comprising sTnI with MAb C5 or a hypoxemia-induced skeletal troponin T (sTnT) peptide fragment with a molecular mass of 28 kDa with MAb JLT-12 (and antibodies disclosed in prior art as capable of binding sTnI and sTnT) in skeletal muscle (including the diaphragm) or alternatively assessing skeletal muscle damage in a subject comprising detecting hypoxemia-induced modified sTnI having a molecular mass of 66 kDa or 26 kDa in urine, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988). These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

First, the claims recite "antibody or antibody fragment", and there is no support in the specification or the literature for an antibody fragment capable of detecting sTnI and

sTnT, but rather the specification recites at detection of sTnI and sTnT fragments (referred to as modified forms in the specification) using MAb C5 and MAb JLT-12 respectively (see p. 8, lines 25-29 to p. 9, lines 1-5, for example). Second, although the specification and the the post-filing date art by the inventors (Simpson et al. J Appl. Physiol. 2000 88: 753-760—submitted by Applicants with Applicants' arguments dated 15 September 2006) provides support for assessing hypoxemia induced muscle damage in skeletal muscle tissue (diaphragm) comprising an immunoblotting assay detecting the 17 kDa sTnI degradation production (peptide fragment) and 42 kDa covalent complex using MAb C5 and the 42 kDa covalent complex using MAb 31-35 (Figure 2) and the 27 kDa sTnT degradation product with MAb JLT-12 and the 66 kDa covalent complex using MAb 4D-11 (see Figure 3), (and modified sTnI in the urine, as shown in Figure 14) neither the specification and the literature teach the detection of other troponin fragments, thus the claims are not enabled for detection of any peptide fragment as broadly recited. This is extremely relevant because according to Simpson et al. (2000), the only degradation products of sTnI and sTnT that occur as a result of hypoxemia induced damage are the 17 kDa and the 27 kDa fragments, respectively. An antibody that measures a different peptide fragment of sTnI or sTnT, i.e. a fragment that is not a degradation product of the proteins that occurs as a result of hypoxemia induced modification, would not be effective at carrying out the claimed methods.

Furthermore, neither the specification nor the literature suggests that the claimed methods can be employed using any biological sample as broadly recited. Indeed, Figures 11, 12, 13 and 14 of the specification, which deal specifically with the detection

of skeletal muscle troponins indicate only that skeletal muscle and urine can be used to assess damage, and Simpson et al. (2000) teach only skeletal muscle. In addition, Simpson et al. (2000) teach at p. 753, right column, last paragraph:

Plasma levels of sTnI and sTnT cannot, however, be used to diagnose respiratory muscle dysfunction until confirmation of both their modification within tissues and their release into the plasma...Our results show that both TnI and TnT were modified, but only in the ***diaphragm*** (emphasis added): these modifications consisted of lower molecular mass degradation products and higher molecular mass covalent complexes consisting of TnI, TnT and possibly troponin C (TnC).

Although Simpson et al. (Clinical Chem. 2002; 48: 1112-1114) suggests that serum levels of sTnI can be detected, Simpson et al. (2002) conclude:

Further work is needed to determine whether changes in fsTnI and/or ssTnI are specific for a given disease (and if so, its severity) and particular muscle types. In addition, the performance of WB-DSA, like any other diagnostic assay using antibodies, is limited by antibody selection and the possibility that modifications of the target protein alter binding affinities and, hence, assay results. It will therefore be necessary to screen different patient cohorts with a variety of antibodies to overcome such limitations. Nevertheless, preferential or selective release of the two isoforms (and their modified products) into blood raises the possibility of improving the differential diagnosis of skeletal muscle injuries or disease, prognosis, and the evaluation of therapeutic effectiveness.

However promising, the art suggests that plasma tests of skeletal muscle damage are not yet enabled.

In addition, the WO document, WO 96/31145, states at p. 18:

The release of troponin components, that is, troponin I, C and T, or components from the contractile apparatus, for example, tropomyosin and actin, from skeletal muscle, due to the normal turnover of skeletal muscle cells, may result in a significant amount of troponin and contractile apparatus components in the blood. Since skeletal muscle mass is much greater than cardiac muscle mass, the troponin components present in the blood of a normal individual may be derived largely from skeletal muscle. The circulating troponin components which are mainly derived from skeletal muscle would bind to cardiac troponin I and T which are released into the blood during a myocardial infarction or events which lead up to creating damaged heart muscle. As muscle damage progresses in an individual the troponin components derived from heart tissue will presumably rise in the blood. Thus, the concentration of troponin components

(bound and free) in the blood from individuals experiencing a myocardial infarction may be differentially derived from both cardiac and skeletal muscle

This document points to the apparent lack of specificity of skeletal troponins in diagnosis of myocardial infarction, thus by extension, a person having undergone an extreme form of exercise (such as a marathon), might have high levels of cardiac and skeletal troponins, which might be more attributable to heart failure as evidenced by recent reports involving cardiac arrest among and increased troponin levels in the serum of competitors in marathons (see New York Times, 7 December 2006; "Is Marathoning Too Much of a Good Thing for Your Heart?", whole document). Finally, with regard to MAb JLT-12, the Ab taught by Simpson (2000) as capable of detecting the sTnT peptide fragment with a molecular mass of 28 kDa, Anderson et al. Circ Res. 1989; 65: 1087-93—see abstract and p. 1091, left column, last paragraph) teach: "[a] monoclonal antibody, MAb JLT-12, raised against a highly conserved epitope of rabbit fast skeletal muscle, recognized all five cardiac as well as five skeletal muscle isoforms," thus raises the possibility in light of recent deaths of cardiac arrest in apparently healthy people during marathons (December 7 2006, NYT) that MAb JLT-12 may not be specific for skeletal damage

Due to the large quantity of experimentation necessary to determine how to detect sTnI and sTnI in any body tissue, identify what compound can be used for detection, the lack of direction/guidance presented in the specification and the absence of working examples directed to the same, the complex nature of the invention as evidenced by the unpredictability of the art (detection of skeletal muscle damage in any body tissue—see discussion above), the contradictory state of the prior art and the

breadth of the claims which fail to recite limitations on the antibodies and fragments detected (for instance, it is not clear what sTnI or sTnT fragments are bound by the compound, however the evidence in the specification and the art shows that there are only two degradation products as a result of hypoxemia-induced skeletal muscle damage), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 80-84 and 92-98 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 16-18, 20-28, 31, 34-35 and 37-41 of copending Application No. 09/419,901 is

maintained for reasons of record. Applicants' did not address this rejection in their response filed 19 December 2006. However, deferral of arguments is not proper; an argument after the claims have been found otherwise allowable that obviousness type double patenting does not exist will not be considered timely. Accordingly, the provisional rejection is maintained.

Claims 80, 82, 83, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96 and 97 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38, 39, 40, 41, 42, 43, 44, 45, and 46 of copending Application No. 11/138,184. Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims are drawn to measuring troponin T and troponin I modification products (which is equivalent to "peptides") in order to assess skeletal muscle damage.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Löfberg et al. (Arch Neurol. 1995; 52: 1210-1214) teach the detection of cardiac TnT for the assessment of skeletal muscle damage, however, in addition to explicitly stating they were detecting cardiac TnT, they teach at p. 1211, left

column, 1st paragraph, "[in] a new immunoassay of cardiac TnT, its cross-reactivity with skeletal muscle was believed to be only 0.5%," thus this reference cannot reasonably be applied as prior art over the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER